Medical Staff Conference

Peptic Ulcer—An Infectious Disease?

Discussant
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These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Perhaps my training in infectious disease has biased me, but I think that infectious agents may be important in many diseases in which they were once thought to play no role. One such disease is peptic ulcer. Recent evidence suggests that a bacterium,* Campylobacter pylori, *may be important in upsetting the balance between the acid and pepsin in gastric secretions and the defense of the gastric mucosa. We are fortunate to have at this conference Dr Peterson from Southwestern Medical Center, Dallas, to review this potentially important organism and the evidence that it contributes to gastritis, dyspepsia, and peptic ulcer disease.*

WALTER L. PETERSON, MD†: Acid and pepsin are present in abundance in the normal human stomach and duodenum. The epithelial cells of the stomach and duodenum are protected from the damaging effects of acid and pepsin by a "balancing" mechanism of mucosal resistance. As long as this balance remains in effect, epithelial integrity remains intact.

Gastroduodenal Mucosal Resistance

The most important factor in mucosal defense against the damaging effects of acid and pepsin may be endogenous prostaglandins.[1,2] Early work by Robert and co-workers showed that administering prostaglandin compounds beforehand could prevent the damaging effects on rat gastric mucosa of various noxious agents.[3] While it was initially thought that this protective effect was related to the antisecretory effect of prostaglandins, Robert and associates later showed that the same protection occurred at doses of prostaglandins that did not reduce acid secretion.[4,5] The ability of prostaglandins in such doses to prevent damage to rat mucosa from a variety of strong irritants was called "cytoprotection." Similar protection against strong irritants can be afforded by pretreatment with mild irritants, rather than prostaglandins.[6,7] Termed "adaptive cytoprotection," this phenomenon is now believed to be a prostaglandin-independent phenomenon.[8]

Great interest has developed in the mechanisms by which prostaglandins protect gastroduodenal mucosa. Two important effects of prostaglandins are the stimulation of mucous and bicarbonate secretion.[9] A mucous gel acts as a barrier to the damaging effects of pepsin and to the diffusion of hydrogen ions from the gastric lumen. The hydrogen ions that are able to penetrate the mucous gel are thought to be neutralized by endogenously secreted bicarbonate. Thus, in the normal state, the milieu just above the epithelial cells is at or near neutrality.[10]

These are only the first lines of defense, however, and the presence of mucus and bicarbonate does not protect all cells from the effects of various damaging agents. Rather, it is now believed that prostaglandins act primarily to maintain mucosal blood flow during a period of injury, a function that may preserve cells deep in mucosal crypts.[11] These cells can then migrate upward and reconstitute damaged superficial epithelium.[12] Whatever the mechanisms, it seems likely that endogenous prostaglandins play a major role in protecting gastroduodenal mucosa from deep tissue injury by acid or pepsin or other damaging agents, at least in animals. The extent to which prostaglandins protect human mucosa is less well understood.

Whenever the balance between acid and pepsin and mucosal resistance shifts toward acid and pepsin, a peptic ulcer may develop. Stated simply, this shift may occur because of excess levels of acid and pepsin, reduced mucosal resistance, or both. Traditional teaching has emphasized the importance of acid (and pepsin) as the cause of this imbalance. For example, persons with high levels of acid secretion, such as in the Zollinger-Ellison syndrome, have a high incidence of duodenal ulceration, whereas prophylactic treatment with agents that reduce gastric acid secretion, such as the H_2-receptor antagonists, reduces the incidence of recurrent ulcer. It is clear, however, that acid and pepsin alone are, in most instances, inadequate to produce a peptic ulcer. For example, most persons with duodenal ulcer have normal levels of acid secretion,[13] and prophylactic treatment with agents that do not affect acid secretion (such as sucralfate) also reduces the risk of ulcer recurrence.[14]

In summary, while acid and pepsin must be present for an ulcer to form, and while high levels of acid secretion in-

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crease the risk of an ulcer developing, the basic mechanism of ulcer formation probably involves a disruption of mucosal resistance.

Disruption of Mucosal Resistance

Reduction of Endogenous Prostaglandins

In humans, evidence that a depletion of endogenous prostaglandins is important in disrupting mucosal protection remains inconclusive. There are, however, several lines of evidence that suggest this may be true:

- Patients with duodenal and gastric ulcer have diminished capacity to synthesize prostaglandins in antral mucosa[15,16];
- Patients with duodenal ulcer have been shown by Isenberg and colleagues to secrete less duodenal bicarbonate than do normal controls, either in the basal state or in response to stimulation with hydrochloric acid[17];
- Administering nonsteroidal anti-inflammatory drugs (NSAIDs), which are believed to be "ulcerogenic," results in reduced levels of prostaglandins in both gastric and duodenal mucosa and a decreased secretion of duodenal bicarbonate.[15,18] Interestingly, epidemiologic studies suggest that there is an increased incidence of gastric ulcer, but not duodenal ulcer, in patients who take NSAIDs.[19,20]

Thus, the role of prostaglandin depletion in the pathogenesis of peptic ulcer disease remains unsettled. It seems likely that a reduction of prostaglandins plays some role, especially in the pathogenesis of gastric ulcer. The mechanisms by which prostaglandin depletion leads to gastric ulcer formation remain unknown.

Helicobacter pylori Gastritis

Investigators have for many years sought an infectious cause of common gastritis. Although occasional reports in the past noted the presence of spiral bacteria in gastric biopsy specimens, the concept did not gain widespread recognition until 1983. In that year, Warren and Marshall, two investigators from western Australia, published letters in *The Lancet* describing spiral bacteria in patients with chronic active gastritis.[21] Because the organisms were curved they were called *Campylobacter,* and because they were found only on gastric epithelium they were called *Campylobacter pyloridis,* later changed to *Campylobacter pylori.* These investigators soon were able to culture the organism and to begin to define its characteristics. Since then, an enormous amount of work by investigators throughout the world has provided insight into the organism itself, where it is found, how it might be transmitted, and what it may do.

Campylobacter pylori is a gram-negative, microaerophilic organism that, while possessing many characteristics of *Campylobacter* species, is not a true *Campylobacter.* For example, *C pylori* produces abundant quantities of urease, an enzyme not present with other *Campylobacter* species. In addition, an analysis of the genetic composition of *C pylori* shows it to be unrelated to *Campylobacter* species such as *Campylobacter jejuni.* Thus, its name was recently changed from *C pylori* to *Helicobacter pylori.* The organism has a particular predilection for gastric epithelium. Its spiral nature and corkscrew-like motility permit it to penetrate the mucous gel overlying gastric epithelium and to set up residence adjacent and adherent to gastric epithelium. While it is never found on intestinal epithelium, it is found in gastric epithelium in the stomach, in the duodenum in areas of gastric metaplasia, and in the esophagus in patients with Barrett's esophagus. Once found, and unless specifically eradicated by antimicrobial agents, *H pylori* infection is persistent, probably for life.

It is not known how *H pylori* is transmitted, and the organism has yet to be isolated except from human tissues. Nevertheless, several lines of evidence point to person-to-person transmission, possibly by the fecal-oral route: The prevalence of *H pylori* is higher in persons from developing countries than in those from industrialized countries[22]; there is a higher prevalence than would ordinarily be expected in persons residing in long-term-care facilities[23]; there has been a report of a family in whom eight members have genetically identical strains of *H pylori,* suggesting person-to-person transmission[24]; and it has been shown that *H pylori* can survive in river water.[25]

The presence of *H pylori* can be determined by several different methods. First, *H pylori* can be seen on biopsy

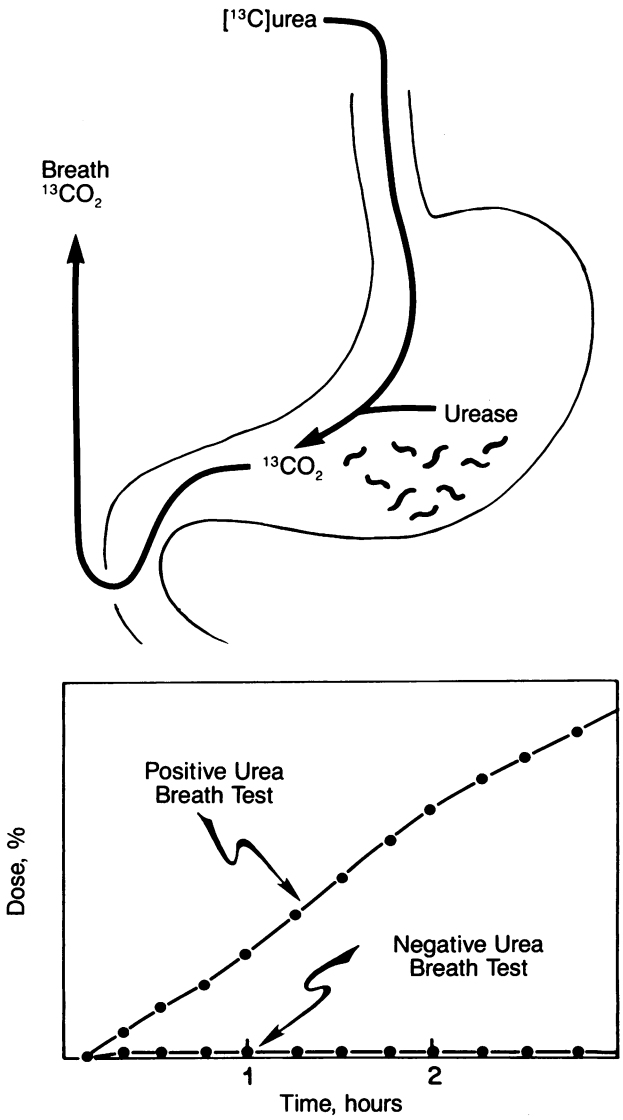

Figure 1.—The diagram and graph show the mechanism of the carbon 13-labeled urea breath test for detecting urease-producing organisms in the stomach. If ingested [^{13}C]urea degrades, producing $^{13}CO_2$, the test is considered positive for urease-producing organisms.

TABLE 1.—*Serum Antibodies to* Helicobacter pylori *Using an Enzyme-linked Immunosorbent Assay**

Antral Culture for H pylori	*Patients, No.*	*Optical Density Value*	
		IgA	*IgG*
Organisms present	29	1.26±0.08	1.71±0.07
Organisms not present	30	0.37±0.07	0.34±0.10

*Data expressed as the mean plus-minus the standard error of optical density (from Perez-Perez et al[29]). Differences are significant at $P<.00001$.

specimens of gastric epithelium using a number of tissue stains.[26] Experienced pathologists can often find the organism simply using the standard hematoxylin-eosin stain. The most sensitive special stain is the Warthin-Starry silver stain, but because this is a tedious and time-consuming technique, the use of the Giemsa stain is recommended when *H pylori* is not found with a hematoxylin-eosin stain. Second, *H pylori* can be cultured from tissue relatively easily now that the techniques have been perfected; and, third, the presence of urease can be detected either by pH-sensitive media or by a breath test, as an indirect means of finding *H pylori*.[27,28] With the breath test, urea is labeled with either carbon 13 or carbon 14 and ingested by the patient. If urease-containing organisms are present in the stomach, the labeled urea is degraded to produce $^{13}CO_2$ or $^{14}CO_2$, which can be detected in expired breath (Figure 1). The advantage of carbon 13 is that it is nonradioactive, but its disadvantage is that a mass spectrometer is needed for the determination. On the other hand, although carbon 14 is radioactive, its presence can be detected without expensive equipment. A final indirect test for *H pylori* is the determination in the blood of antibodies to the organism. Persons with *H pylori* determined by histologic examination, culture, or the urea breath test will almost invariably have high titers of immunoglobulin G and A antibodies to *H pylori* (Table 1).[29] Occasionally, however, a patient will have antibodies to *H pylori* but the organism will not be in the stomach. These antibodies undoubtedly reflect a previous infection with the organism in a person whose stomach has been cleared of the organism itself. One intriguing mystery surrounding *H pylori* is how it can elicit such a substantial antibody response and yet continue to flourish in its ecologic niche.

Numerous investigators have confirmed the close association between *H pylori* and histologically determined gastritis. In fact, when *H pylori* organisms are present in the antrum, gastritis is always found. The association is not so tight when the body mucosa is assessed. Here, in our experience, about 10% of patients with *H pylori* will have histologically normal mucosa. The association between *H pylori* and gastritis, however, does not prove a cause-and-effect relation. Unfortunately, there is no reliable animal model for *H pylori* gastritis. Two persons have, after their stomachs were rendered hypochlorhydric with an H_2-receptor antagonist, ingested large inocula of *H pylori*. In each instance, it was reported that gastric mucosa that had previously been normal became inflamed and now harbored *H pylori*. Beyond these two cases, the evidence to support *H pylori* as a pathogen causing gastritis is indirect, albeit persuasive. This evidence includes two observations. First, *H pylori* is seldom found in patients with gastritis of other known causes such as eosinophilic gastritis, Crohn's disease, or the atrophic gastritis associated with pernicious anemia. One explanation for the absence of *H pylori* in patients with pernicious anemia may

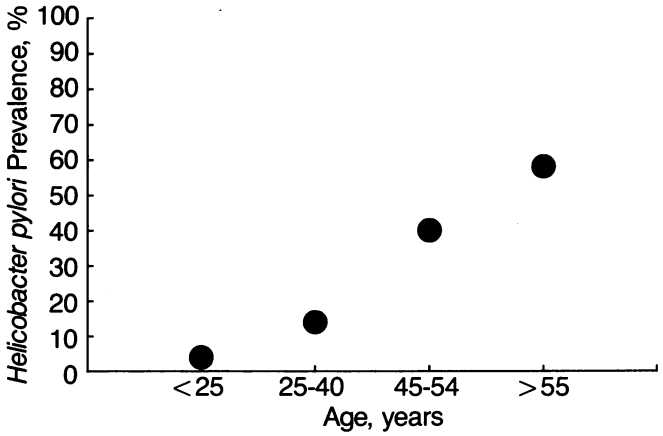

Figure 2.—The graph shows the prevalence of *Helicobacter pylori* in 73 asymptomatic healthy humans as determined either by histologic examination or by culture (W.L.P., unpublished observations).

be that such persons have extensive intestinal metaplasia, where *H pylori* is not found. Second, studies have now shown that eradicating *H pylori* with antimicrobial therapy is associated with an abatement or resolution of gastritis histologically.[30] It remains possible, however, that agents that eradicate *H pylori* may have some separate, intrinsic effect on mucosal inflammation. Further work with *H pylori* will be greatly enhanced by the development of either a convenient animal model or perhaps an ex vivo system using tissue culture techniques.

If it is accepted that *H pylori* does indeed produce an inflammatory response, the question remains, how does it do it? Preliminary studies suggest that *H pylori* may release a toxin that elicits an inflammatory response. Other studies suggest that ammonia produced from the metabolism of urea under the influence of urease may be cytotoxic. In one study using cultured gastric epithelium, administering acetohydroxamic acid, a urease inhibitor, reduced the degree of inflammatory response to *H pylori*.[31] Intensive efforts are being made to learn more about the pathogenicity of *H pylori* including such factors as its adherence to the mucosa and the elaboration of a toxin.

Helicobacter pylori gastritis is found in normal healthy persons. The prevalence in young persons tends to be low, but it increases linearly with age so that the prevalence of *H pylori* gastritis is high in healthy older subjects (Figure 2). There are several groups of patients in whom the prevalence of *H pylori* is higher than would be expected for a given age. Stated another way, these persons become colonized at an earlier age. For example, the prevalence of *H pylori* is higher at a given age in blacks and Hispanics than in whites.[32,33] Although this may be to some degree related to socioeconomic factors, it is possible that genetic factors also play a role. Patients with gastric and duodenal ulcer disease also have a higher prevalence of *H pylori* gastritis than do age-matched controls.[34] Finally, some studies suggest that patients with nonulcer dyspepsia have a higher prevalence of *H pylori* than normal, although other studies do not.

Because of the higher prevalence of *H pylori* in patients with various peptic diseases, it has been suggested that the organism may play a role in their pathogenesis. Again, because there is no animal model for *H pylori* gastritis-associated peptic ulcer disease, all evidence to support this association is indirect. Such evidence includes the following: First, patients with duodenal and gastric ulcer disease have a high

prevalence, at an early age, of *H pylori* gastritis[34]; second, it is thought that duodenal ulcers occur in areas of gastric metaplasia. Such tissue is frequently noted to be inflamed and to harbor *H pylori*; third, in two controlled trials recently it was suggested that eradicating *H pylori* leads to a prolonged remission in patients with duodenal ulcer disease.[35,36] In one of these studies, 35 patients with duodenal ulcer were treated and their ulcers healed with the use of bismuth subsalicylate alone or with bismuth subsalicylate plus an antibiotic.[36] Of 25 of those patients in whom *H pylori* was eradicated at the time of ulcer healing, ulcers recurred during the next 12 months in 6. On the other hand, 7 of 10 patients in whom *H pylori* was still present after therapy had an ulcer recurrence during the next 12 months.

While these data are provocative, several observations suggest that more evidence is required before the hypothesis is accepted. First, these studies were not well-blinded. Second, there is poor correlation when using "anti-*H pylori*" regimens between the eradication of the organism and ulcer healing, as opposed to ulcer recurrence. Moreover, an adequate number of patients has not been studied to prove that any salutary long-term effect of using bismuth with or without antibiotics is due to *H pylori* eradication rather than an intrinsic effect of the medications on gastroduodenal epithelium. Another factor is that agents that have no effect on *H pylori* (such as H_2 blockers, prostaglandins, sucralfate) heal ulcers effectively. In addition, in the stomach, *H pylori* gastritis is rather diffuse, yet ulcers are focal. Finally, it is well known that after healing, ulcers recur only periodically despite the fact that levels of gastric acidity remain relatively constant, as does the presence of *H pylori*. Thus, a role for *H pylori* in duodenal ulcer disease remains unproved. Even if *H pylori* proves to be a factor predisposing to the development of duodenal ulceration, it certainly is not the only factor. That is, although acid, and perhaps *H pylori*, are both necessary for the pathogenesis of duodenal ulceration, there are certainly other important factors.

Helicobacter pylori gastritis has also been suggested by some as a cause of nonulcer dyspepsia, but there are no convincing randomized, double-blind studies to suggest that symptoms of nonulcer dyspepsia are lessened more often with therapy directed toward *H pylori* than if a placebo is used. While it is possible that there may be a subset of patients with nonulcer dyspepsia whose symptoms are related to the presence of *H pylori* gastritis, this issue remains unclear.

The questions frequently arise whether *H pylori* should be treated, in whom, and how. At this stage of our knowledge, and until we have a much better grasp of the role of *H pylori* gastritis in disease, therapy should be limited to randomized controlled trials or to special circumstances. The latter include the two following situations. First are patients with nonulcer dyspepsia for whom all other forms of therapy have failed but who remain debilitatingly symptomatic. The other situation is patients with duodenal ulcer (but not Zollinger-Ellison syndrome) in whom medical therapy has failed but for whom surgical therapy is not desirable. It cannot be emphasized strongly enough that the treatment of *H pylori* in these patients is not based on scientific evidence of efficacy. Although such patients should, if possible, be entered into randomized controlled trials, the practical reality is that those trials are conducted in only a few centers, which is not much help to physicians with such patients in their practices. Therefore, until data confirm or refute the efficacy of antimicrobial therapy for *H pylori*, the following advice is offered: For patients with intractable nonulcer dyspepsia, an initial empiric course of bismuth subsalicylate is reasonable because the drug appears to be safe. In the United States, Pepto-Bismol,* two tablets four times a day for four weeks, can be tried. If this fails, and if an antral biopsy discloses *H pylori* gastritis, antibiotic therapy can be added for one to two weeks. Indeed, data strongly suggest that bismuth therapy alone results in long-term eradication in only about 25% of patients. An effective antibiotic regimen has not been firmly established, but it appears that adding metronidazole to bismuth therapy will produce an eradication in as many as 80% of patients. For patients with duodenal ulcer who would ordinarily be considered for surgical therapy but for whom the operative risk is high or they have refused, a trial of bismuth plus metronidazole may be warranted. Because of the possibility of bismuth intoxication if used long term, bismuth compounds should be used for only short periods of time.

Helicobacter pylori gastritis has provided an exciting new area of investigation into the pathogenesis of peptic ulcer disease. Many questions remain, however. We need to know more about how *H pylori* is transmitted, what its epidemiologic patterns are, why *H pylori* has a predilection for gastric and not intestinal epithelium, exactly how the organism elicits an inflammatory response, to what extent species variation from one strain of *H pylori* to another is important in terms of disease states, and what the role of *H pylori* is in disease states. An animal model or ex vivo system to study *H pylori* would be enormously helpful, and larger, more stringently designed, randomized controlled trials need to be done. Until these issues are addressed, physicians should view the importance of *H pylori* and its treatment with caution.

*Pepto-Bismol has not been approved by the US Food and Drug Administration for the treatment of duodenal ulcer.

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